REMARKS

Reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. §1.112 are respectfully requested.

Claims 1-10, 12, 22, 26, 40, 42-44, 46, 50, 53-54, 56, 58 and 63-134 are pending in the application. Of these, claims 1-10, 12, 40, 43, 44, 46, 50, 70-84, 98, 99, 104-105, 111-114 and 123-126 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 22, 26, 42, 53-54, 56, 58, 63-69, 85-87, 100-103 and 106-110, 115-122 and 127-134 are under consideration and stand rejected.

No amendment has been made to the claims.

Interview summary

Applicants thank the Examiner for the courtesy of an interview on February 11, 2009. During the interview, the prior art relied upon in the pending rejections and the general state of the art was discussed in relation to the rejection under 35 USC § 103(a). No agreement was reached with regard to the rejection under 35 USC § 103(a). The rejection of the claims under 35 USC § 112, first paragraph as failing to comply with the written description requirement was also discussed. The Examiner indicated that the rejection under 35 USC § 112, first paragraph would be withdrawn. Nevertheless, for the sake of completeness, the rejection is addressed in the remarks that follow.

Claim rejections- 35 USC §112

Claims 22, 26, 42, 53-54, 56, 58, 63-69, 85-87, 100-103 and 106-110, 115-122 and 127-134 remain rejected under 35 USC §112, first paragraph, as allegedly failing to comply with the written description requirement. The rejection is traversed.

The Examiner has acknowledged that Applicant provided various publication defining introns and amended the claims to recite introns, implicating those involved in excision or splicing process, rather than intronic sequences. See, OFFICE ACTION mailed September 19, 2008 at 3 line 17 to 4 line 2. The Examiner indicated that the examples provided in the initial disclosure, however, are (*sic*) representative of the genus of compounds and plants claims. See, OFFICE ACTION mailed September 19, 2008 at 4 line 11-13. However, the Examiner concluded that Applicants, having providing the examples described in the Specification, were not in possession of the broad array of compounds or plants currently claimed, at the time of filing. See, OFFICE ACTION mailed September 19, 2008 at 4 line 2-5. The conclusion of the Examiner appears to be directed at the general breadth of the claims. The Examiner does not explain any particular aspects of the present claims that are not adequately described.

During the interview conducted February 11, 2009, the Examiner indicated that the reason for maintaining the rejection of the claims under 35 USC §112, first paragraph was based on the observation that the declarations of prior invention under 37 C.F.R. § 1.131 provided with the Reply filed May 1, 2008 described a limited number of examples of actual reduction to practice of embodiments of the invention. The Examiner considered that the declarations pursuant to 37 C.F.R. § 1.131 did not provide complete written description of the claimed genus. Applicants pointed out that there is no requirement for declarations submitted for the purpose of showing prior invention pursuant to 37 C.F.R. § 1.131 to satisfy the

requirements of 35 U.S.C. § 112, first paragraph. A 37 CFR §1.131 affidavit or declaration must establish possession of something falling within the claim (such as a species of a claimed genus), in the sense that the claim as a whole reads on it. M.P.E.P. § 715.02 (citing In re Tanczyn, 347 F.2d 830, 146 USPQ 298 (CCPA 1965)). Thus, the scope of the declarations presented pursuant to 37 C.F.R. § 1.131 are not relevant to the question of sufficiency under 35 U.S.C. § 112, first paragraph.

Applicants pointed out that the question of compliance with 35 U.S.C. § 112, must be decided with respect to the content of the Specification, and how that Specification would have been understood by a person of ordinary skill in the art at the time the application was filed. Applicants have submitted substantial evidence that every element of the claimed invention has been adequately described when considered in light of the knowledge available to a person of ordinary skill at the time the application was filed. During the interview, the Examiner agreed that the rejection under 35 USC §112, first paragraph would be withdrawn.

In as far as the Examiner may reconsider the agreement reached, Applicants maintain their previous position as supported by the declaration of Drs Dennis, De Block and Schoffield that a person of ordinary skill in the art would have been well aware of the interchangeability of the intron specifically exemplified in the Application for any other intron sequence and the generally sufficient description of all the elements that are combined in the present invention. Indeed, a person of ordinary skill in the art would have been well aware of the facts that may different introns existed in eukaryote genes, that the introns were removed from the primary transcripts by a universally conserved RNA splicing pathway, and that the relevant structural features for the removal of introns were highly conserved between different introns and well known. See, DECLARATION OF DENNIS at page 3, paragraph 14; DECLARATION OF DEBLOCK at page 3 paragraph 17; DECLARATION OF SCHOFFIELD page 7,

paragraphs 29-30. In view of the conserved nature of the important structural features for the removal of introns, and further in view of the fact that introns are removed from the primary RNA transcript, Applicants submit that any secondary considerations such as nucleotide sequence or size of the introns are not critical for the invention as currently claimed. Furthermore, the Affiants in this application have testified to the general knowledge of a representative number of potential target sequences and other elements of the claimed invention so that persons of ordinary skill in the art would not have required further description to have recognized that the inventors were in possession of the full scope of the claimed invention.

Applicants further point to the accompanying declaration by Dr Michael Metzlaff (submitted concurrently herewith), stating his opinion that the application described the invention in sufficient detail to demonstrate that the inventors had a complete conception of the invention and described it sufficiently such that a person of ordinary skill in the art would have understood what the invention was and how it was distinguished over the prior art . DECLARATION OF METZLAFF page 4, paragraph 14. Dr. Metzlaff was a person working in the filed at the time of the invention and adds yet another voice to the chorus of experts that testify a person of ordinary skill in the art would have recognized from the application as filed that the inventors were in possession of the invention that is currently claimed.

Withdrawal of the rejection is respectfully requested.

Claim rejections- 35 USC §103

Claims 22, 26, 42, 53-54, 56, 58, 63-69, 85-87, 100-103 and 106-110, 115-122 have been rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Flavell, Metzlaff

et al. and Stam et al., the combination in view of Brown et al. Luskey et al. The rejection is traversed.

The Examiner alleges Flavell et al. (Proc. Natl. Acad. Sci., Vol 91, pages 3490-3496, 1994) discloses plants, eukaryotic cells and chimeric DNA comprising an operable promoter, transcription termination and polyadenylation region and further comprising a DNA region encoding a region capable of forming a double stranded RNA stem by base pairing between regions with a sense and antisense nucleotide sequence, which sense nucleotide sequence includes at least 10 consecutive nucleotides having 100% sequence identity with at least 10 consecutive nucleotides having 100% sequence identity with said at least 10 consecutive nucleotides of the sense sequence. See, OFFICE ACTION mailed September 19, 2008 at 6. The Examiner further contends that Metzlaff et al. (Cell, Vol. 88 pages 845-854, 1997) teaches plants, eukaryotic cells and chimeric DNA comprising an operable promoter, transcription termination and polyadenylation regions, and further comprising a DNA region encoding a region capable of forming a double stranded RNA by base pairing between regions with a sense and an antisense nucleotide sequence. See, OFFICE ACTION mailed September 19, 2008 at 7. The office further alleges that Stam et al. (Annals of Botany, Vol 79., pages 3-12, 1997) discloses plants, eukaryotic cells and chimeric DNA comprising an operable promoter, transcription termination and polyadenylation region and further comprising a DNA region encoding a region capable of forming an artifical hairpin RNA structure with a double stranded RNA stem by base pairing between regions with a sense and antisense nucleotide sequence, which sense nucleotide sequence includes at least 10 consecutive nucleotides having 100% sequence identity with at least 10 consecutive nucleotides having 100% sequence identity with said at least 10 consecutive nucleotides of the sense sequence. See, OFFICE ACTION mailed September 19, 2008 at 7.

The Examiner admits that the primary references of Flavell, Metzlaff et al. and Stam et al. do not teach double stranded hairpin constructs in their inverted repeats, nor do they teach the insertion of an intron in their double stranded inhibitory constructs. See, OFFICE ACTION mailed September 19, 2008 at 7, last paragraph.

However, the Examiner contends that it would have been obvious to one of ordinary skill in the art at the time of the invention was made to alter the expression of a target gene of known sequence comprising the introduction of nucleic acids comprising sense and complimentary antisense sequences of the target genes operably linked to a promoter and which are optionally expressed on separate or the same expression construct, because this approach to gene silencing had been proposed and studied previously by Flavell, Metzlaff et al. and Stam et al. See, OFFICE ACTION mailed September 19, 2008 at 8. To remedy the admitted deficiency of the primary references in teaching double stranded hairpin constructs, the Examiner alleges that One of ordinary skill in the art would have been motivated to design inverted repeats as a single molecule to test it inhibitory capacity because expression of a single, contiguous self annealing construct would provide for more efficient self annealing compared to tow separately expressed self annealing molecules, applying scientific logic to the teachings of Flavell, Metzlaff and Stam. See, OFFICE ACTION mailed September 19, 2008 at 9, lines 3-9.

Applicants respectfully disagree with the Examiner's reading of the Metzlaff, Stam and Flavell publications. The Examiner's reading of the references appears to be influenced by application in hindsight of knowledge that was disclosed only after the present invention was made.

The Examiner's attention is directed to the accompanying declaration by Dr Michael Metzlaff pursuant to 37 C.F.R. § 1.132. Dr. Metzlaff was an expert in the field of gene-

silencing at the time the invention was made and is co-author of one of the primary references relied on. Dr. Metzlaff provides his testimony concerning what the references would have taught a person of ordinary skill in the art given the general state of the art the time the invention was made.

Dr Michael Metzlaff testifies that the publications by Flavell, Metzlaff et al. and Stam et al (or other contemporaneous publications related to the field of co-suppression) did not contemplate that double stranded RNA structures formed between antisense RNA and the sense mRNA could be a triggering agent in gene silencing. DECLARATION OF METZLAFF at ¶ 9. Dr Metzlaff further testifies that at that point in time the favourite hypothesis to explain the co-suppression mechanism of action included the model that co-suppression was mediated through the involvement of an antisense molecule generated via a unknown mechanism from the sense RNA. The antisense RNA molecule could then form a dsRNA intermediate with the targeted mRNAs which were thus tagged for degradation. DECLARATION OF METZLAFF at ¶ 14. According to this model, the antisense RNA is the pivotal molecule in gene-silencing.

Dr Metzlaff also declares that a person of ordinary skill in the art understanding the proposed models for gene silencing would not have included a sense and antisense RNA strand in one single molecule to obtain more efficient self annealing. This is because the proposed models and prevailing wisdom considered a antisense strand to be the operative gene-silencing triggering molecule. More efficient self annealing would sequester the antisense strand by base-pairing with the sense strand, which would be contrary to the mechanisms proposed in the cited papers and generally understood at the time. DECLARATION OF METZLAFF at ¶ 9. He also testifies that he was a person of at least ordinary skill at the time and certainly would never have contemplated deliberately introducing

complimentary sense and antisense sequence of a target gene which can form a double stranded RNA molecule to increase the efficiency of gene silencing based upon these papers or the general understanding in the art at the time. DECLARATION OF METZLAFF at ¶ 9.

Dr Metzlaff concludes that Flavell, Stam and Metzlaff all emphasize the importance of the complementary RNA/antisense RNA as the central effector molecule in gene silencing and reiterates that accordingly it would not be logical to enhance the efficiency of gene silencing by simultaneous introduction of a sense and antisense RNA molecule capable of forming a duplex RNA with each other, since this sense RNA molecule would compete with the targeted mRNA molecule for duplex formation with the active antisense molecule triggering the gene-silencing phenomenon. The competition would even be more severe if the introduced sense and antisense RNA would be present in one molecule, as such intramolecular duplex formation would be favored over intermolecular duplex formation. DECLARATION OF METZLAFF at ¶ 31. Therefore, Dr Metzlaff expresses his opinion that it would **not** have been obvious to one of ordinary skill in the art to derive from the Flavell, Metzlaff et al. and Stam et al. publications (or other contemporaneous publications in the field of co-suppression in plants) that expression of target genes in a cell can be inhibited by the introduction of chimeric genes expressing sense and complimentary antisense sequences of the target gene (either from separate constructs or from the same construct) which can form a double stranded RNA molecule. DECLARATION OF METZLAFF at ¶ 32.

Dr Metzlaff's declaration thus refutes the Examiner's reading of the primary references as teaching modification of the expression of a target gene of known sequence comprising the introduction of nucleic acids comprising sense and complimentary antisense sequences of the target genes operably linked to a promoter and which are optionally expressed on separate or the same expression construct. Furthermore, Dr Metzlaff's

declaration traverses the Examiner's opinion that a person of ordinary skill in the art understanding the proposed models for gene silencing would have included a sense and antisense RNA strand in one single molecule to obtain more efficient self annealing.

The secondary references by Brown (US 5,859,347) and Lusky (6,350,575) are only relied upon to demonstrate that in certain circumstances introns had been used in expression constructs in the prior art. However, since the secondary references are silent with regard to teaching modification of the expression of a target gene of known sequence comprising the introduction of nucleic acids comprising sense and complimentary antisense sequences of the target genes operably linked to a promoter, they do not remedy the deficiencies of the primary references. Moreover, the inaptness of these references has been previously addressed by Applicants. Borwn relates to increasing protein expression by improving translation efficiency whereas Lusky relates to use of introns to better conform a construct to capsid capacity for more efficient production of viral particles. The references provide reasons for the inclusion of introns in distinctly different kinds of gene constructs that are simply not applicable to the present invention. Applicants therefore also maintain all the arguments made in previous responses concerning the unobviousness to further enhance gene silencing efficiency by inclusion of an intron within the expression constructs for gene silencing.

For the reasons elaborated herein, the currently claimed invention would not have been obvious over over Flavell, Metzlaff et al. and Stam et al., the combination in view of Brown et al. Luskey et al. Accordingly, withdrawal of the rejection is respectfully requested.

Request for rejoinder of process claims 1-10, 12, 40, 43, 44, 46, 50, 70-84, 98, 99, 104-105, 111-114 and 123-126.

The withdrawn process claims 1-10, 12, 40, 43, 44, 46, 50, 70-84, 98, 99, 104-105, 111-114 and 123-126 include all the limitations of the product claims under consideration. Accordingly, Applicant requests that the restriction between withdrawn process claims 1-10, 12, 40, 43, 44, 46, 50, 70-84, 98, 99, 104-105, 111-114 and 123-126 and product claims 22, 26, 42, 53-54, 56, 58, 63-69, 85-87, 100-103 and 106-110, 115-122 is withdrawn. The process claims should be considered for rejoinder, and further fully examined for patentability in accordance with 37 CFR 1.104.

Pending Petition To Correct Inventorship

The Examiner is respectfully reminded that a Petition to Correct Inventorship was filed in this application on September 13, 2006 and that further supporting documentation in the form of a copy of a Declaration pursuant to 37 C.F.R. § 1.63 without handwritten corrections was filed on December 1, 2006. An indication that the petition has been granted is respectfully requested.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned concerning such questions so that the prosecution of this application may be expedited.

The Director is hereby authorized to charge any appropriate fees that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: March 19, 2009

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